Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)

Decision Summary

Emerging safety concerns (thrombosis, cardiovascular events, tumor progression, reduced survival) have prompted CMS to review its coverage of erythropoiesis stimulating agents (ESAs). The initial scope of this national coverage analysis (NCA) was "non-renal" uses. Current non-renal indications for ESA use that are approved by the FDA are: cancer treatment related anemia (erythropoietin, darbepoetin), AZT-induced anemia in HIV-AIDS (erythropoietin only), and prophylactic use for select patients undergoing elective orthopedic procedures with significant expected blood loss (erythropoietin only) (Aranesp® drug label; Procrit® drug label). Because there is a preponderance of emerging data for ESA use in the oncology setting, the focus of the NCA will be ESA use in cancer and related conditions. The other non-renal uses may be addressed in future NCAs. We expect that our future reviews will also include the more adequately powered study of ESA use in spine surgery patients. In the interim, local Medicare contractors may continue to make reasonable and necessary determinations on all non-cancer and non-neoplastic conditions as well as other non-renal uses of ESAs.

CMS is seeking public comment on our proposed determination that there is sufficient evidence to conclude that erythropoiesis stimulating agent (ESA) treatment is not reasonable and necessary for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on their underlying disease or because the underlying disease increases their risk of adverse effects related to ESA use. These conditions include:

1. any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
2. the anemia of myelodysplasia
3. the anemia of myeloid cancers
4. the anemia associated with the treatment of myeloid cancers or erythroid cancers
5. the anemia of cancer not related to cancer treatment
6. any anemia associated with radiotherapy
7. prophylactic use to prevent chemotherapy-induced anemia
8. prophylactic use to reduce tumor hypoxia
9. patients with erythropoietin-type resistance due to neutralizing antibodies
10. patients with treatment regimens including anti-angiogenic drugs such as bevacizumab
11. patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor
12. anemia due to cancer treatment if patients have uncontrolled hypertension
13. patients with thrombotic episodes related to malignancy

We also propose that ESA treatment is only reasonable and necessary under specified conditions for the treatment of anemia in those types of cancer in which the presence of erythropoietin receptors on either normal tissue/cell lines or malignant tissue/cell lines has been reported in the literature. These cancer types include but are not necessarily limited to:

- bone (sarcoma),
- hepatic,
- pancreatic (exocrine),

- brain-neurologic,
- breast,
- cervical,
- colo-rectal,
- gastric,
- head-and-neck (squamous cell),
- lung,
- lymphoma
- melanoma,
- multiple myeloma
- muscle including cardiac,
- ovarian,
- prostate,
- retinal, and
- uterine.

For patients undergoing treatment for these cancers, we propose ESAs are reasonable and necessary with the following limitations:

1. the hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be <9 g/dl/27% in patients without known cardiovascular disease and <10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion (The latter patients should be alerted to the increased potential for thrombosis and sequelae.) (We suggest that patients, especially those in the latter category, be alerted to the increased potential for thrombosis and sequelae.)
2. the maximum covered treatment duration is 12 weeks/year;
3. the maximum covered 4 week treatment dose is 126,000 units for erythropoietin and 630 µg for darbepoietin;
4. continued use of the drug is not reasonable and necessary if there is evidence of poor drug response (hemoglobin/hematocrit rise <1 g/dl/<3%) after 4 weeks of treatment;
5. continued administration of the drug is not reasonable and necessary if there is an increase in fluid retention or weight (5 kg) after 2 weeks of treatment; and
6. continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin/hematocrit >1 g/dl/>3% after 2 weeks of treatment.

Local contractors may make reasonable and necessary determinations for all uses of ESA therapy for beneficiaries with cancer whose condition is not addressed above.

We are requesting public comments on this proposed determination pursuant to section 1862 as revised by 731 of the Medicare Modernization Act. In light of the issues discussed in our review of the evidence and serious safety concerns voiced in the May 10, 2007 FDA Oncologic Drugs Advisory Committee (ODAC) meeting we are also interested in public comment on whether coverage for ESA therapy for Medicare beneficiaries with cancer should occur only within appropriately designed clinical research studies where informed consent and safety monitoring can be assured. After considering the public comments and any additional evidence, we will make a final determination and issue a final decision memorandum.

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Proposed Decision Memo

TO:	Administrative File: CAG #000383N The Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions
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SUBJECT: Proposed Coverage Decision Memorandum for the Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions

DATE: May 14, 2007

I. Proposed Decision

Emerging safety concerns (thrombosis, cardiovascular events, tumor progression, reduced survival) have prompted CMS to review its coverage of erythropoiesis stimulating agents (ESAs). The initial scope of this national coverage analysis (NCA) was “non-renal” uses. Current non-renal indications for ESA use that are approved by the FDA are: cancer treatment related anemia (erythropoietin, darbepoetin), AZT-induced anemia in HIV-AIDS (erythropoietin only), and prophylactic use for select patients undergoing elective orthopedic procedures with significant expected blood loss (erythropoietin only) (Aranesp® drug label; Procrit® drug label). Because there is a preponderance of emerging data for ESA use in the oncology setting, the focus of the NCA will be ESA use in cancer and related conditions. The other non-renal uses may be addressed in future NCAs. We expect that our future reviews will also include the more adequately powered study of ESA use in spine surgery patients. In the interim, local Medicare contractors may continue to make reasonable and necessary determinations on all non-cancer and non-neoplastic conditions as well as other non-renal uses of ESAs.

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II. Background

In this section, we describe the technological developments that gave rise to the use of genetically engineered (recombinant) erythropoietin and related ESAs. We then describe the anemia for which ESAs are prescribed in oncologic conditions, with an emphasis on solid tumors which constituted the majority of tumors in the studies upon which FDA approval was based. For purposes of this discussion, therapy for a medical condition includes treatment for the signs and symptoms of the underlying condition and treatment for the signs and symptoms of oncologic treatment. Though we have tried to simplify the discussion for the lay reader, the topic is scientifically complex and we believe that an overly simplistic treatment would ultimately be detrimental to the understanding of our review.

A. Biochemical Background

Erythropoietin is a 34-kDa glycoprotein produced primarily, but not exclusively, in the kidney and to a lesser extent in the liver (Dame 1998, Ebert 1999, Eckardt 1992, 2005, Jelkmann 2001, Koury 1991, Moritz 1997, Rankin 2007, Tam 2006, Zanjani 1981). The native protein is a 193 amino acid peptide sequence from which a 27 amino acid peptide leader sequence is removed from the N-terminus. An arginyl residue at the carboxyl terminus also appears to be cleaved during post-translation processing. The mature protein consists of a 165 amino acid backbone with 2 disulfide bonds, three N-linked carbohydrate chains, and one O-linked carbohydrate chain. The major side chains, sialated tetraantennary saccharides, contribute to in vivo stability (Elliott 1996, Faulds 1989, Narhi 1991, 1997, 2001, Sytkowski 1991, Toyoda 2000).

In the classic hormone pathway, erythropoietin regulates erythrocyte production by stimulating progenitor cell proliferation and differentiation in the bone marrow. Hypoxia plays a major role in the feedback loop (Ebert 1999). Erythropoietin activity is mediated through the erythropoietin receptor. The expression of erythropoietin receptors on erythroid progenitor cells is well known (Constantinescu 2003, D'Andrea 1989, 1991; Fraser 1988, Jones 1990; Winkelman 1990). Less well appreciated is the presence of erythropoietin receptors on other tissues including cardiac myocytes, macrophages, neurons, vascular endothelial cells (Anagnostou 1990, 1994; Digicaylioglu 1995; Haroon 2003; Lappin 2003, Masuda 1993; Wright 2004), and cancers/cancer cell lines (bone sarcoma, breast, cervical, colon, gastric, head-neck [squamous cell], hepatoblastoma, melanoma, ovarian, pediatric, renal, retinal, and uterine (Acs 2001, 2002, 2003; Arcasoy 2003, 2005; Batra 2003; Farrell 2004, Fraser 1989; Henke 2006, Jones 1990, Kumar 2006, Lappin 2003, Masuda 1993, Mioni 1992, Ogilvie 2000 Ribatti 2003; Selzer 2000; Westenfelder 2000; Yasuda 2001, 2006). Also less well understood is the role erythropoietin appears to play in angiogenesis (blood vessel formation) in wounds and the female reproductive tract (Haroon 2003; Yasuda 1998). Tumors differ in the extent of erythropoietin receptor and erythropoietin expression (Lai 2005). Metastatic tumors may express erythropoietin receptors and erythropoietin to a greater extent than primary tumor (Lai 2005). Erythropoietin, through its receptor, appears to activate several signaling pathways that are operational in cancer JAK-STAT (Janus kinase-Signal Transducer and Activator of Transcription), MAPK (mitogen-activated protein kinase), NFκ B (nuclear factor-kappa B), and PI3K-Akt (phosphatidylinositol 3-kinase-Akt) (Barber 1994, 1997, Bittorf 2001, Constantinescu 2003, Kumar 2006, Lai 2005, Lester 2005, Linnekin 1992, Mohyeldin 2005, Xia 1996)

Several forms of recombinant human erythropoietin have been developed (Table 1). They differ in their carbohydrate structure. The most common species are erythropoietin-alpha and beta (Deechongkit 2006, MacDougall 2002). The pharmacokinetic half-life of these products is 6 to 8 hours after IV injection (Halstenson 1991). Because the pharmacodynamic response on the bone marrow is prolonged, dosing regimens vary from 3 times weekly to once weekly. Peak serum levels are higher with the weekly dosing regimens (Cheung 1998, 2001, FDA Procrit Clinical Pharmacology Review 2004, Kryzanski 2005, Ramakrishnan 2004). Dosing via the intravenous route may require 10 to 25% more drug for the same hematologic effect compared to subcutaneous administration (Kaufman 1998, McMahon 1990, Salmonson 1990). The erythropoietin molecule has been modified by the addition of 2 N-linked carbohydrate chains to form darbepoietin. The additional sialic acid residues decrease pharmacokinetic clearance by the body and permit weekly and semi-weekly dosing (MacDougall 1999). More recently, the erythropoietin molecule has been modified by the addition of a methoxy-poly-ethylene glycol polymer chain (pegylation) via a succinimidyl butanoic acid linker (MacDougall 2003, 2005). These changes further decrease pharmacokinetic clearance by the body and permit weekly and even monthly dosing (MacDougall 2005). Although the molecular modifications decrease the affinity of the compound for the erythropoietin receptor in vitro, the increased residence time results in increased exposure of the compound to the erythropoietin receptor and increased erythropoietin-type activity in vivo (MacDougall 2003).

Recombinant erythropoietin was initially used as a replacement for missing hormone in select patients with anemia of end-stage renal disease. Use of ESAs has been extended to a variety of anemic conditions including the anemia of chronic renal disease (not yet on dialysis), anemia secondary to chemotherapy of solid tumors, anemia secondary to AZT therapy, and prophylactic use during the peri-operative period to reduce the need for allogenic blood transfusions (Aranesp label, Danna 1990, Fischl 1990, Laupacis 1993, Procit label). Exploratory work for ESA use treating the anemia of solid tumors and the chemotherapy-induced anemia of hematologic cancers has been undertaken (Dammacco 2002, Gagnon 2003, Patrick 1996, Quirt 2001, Straus 2003)

Table 1: Erythropoiesis Stimulating Agents

Compound	Drug Names	Manufacturer	Production Site	Supplier	Distribution Sites

Compound	Drug Names	Manufacturer	Production Site	Supplier	Distribution Sites
Erythropoietin- α	Epogen	Amgen	USA	Amgen	USA
Erythropoietin-α	Procrit	Amgen	USA	Ortho Biotech	USA
Erythropoietin-α (w/o serum albumin)	Eprex Epypo Epopen Epoxitin Globuren	J&J subsidiary (Otho Biologics)	Puerto Rico	Cilag Janssen	Europe, Canada (Some of these no longer distributed)
Erythropoietin-β	(Neo)Recormon	Roche	Germany	Roche	Europe Recormon no longer marketed
Erythropoietin-β	Erantin			Boehringer Mannheim (Spain), Roche (Spain)	Discontinued or no longer marketed
Erythropoietin-β	Epoch	Chugai	Japan		Under development
Erythropoietin-δ In human cell lines	Dynepo Gene Activated Erythropoietin	Aventis Transkaryotic Therapies		Shire	Europe (not yet launched) Patent issues
Erythropoietin-Ω	Epomax Hemax Hemax-Eritron	Baxter		Cryopharma (Mexico) Lek (Czech)	Countries outside USA

Compound	Drug Names	Manufacturer	Production Site	Supplier	Distribution Sites
				Sidus (Argentina) Bio Sidus (Thailand) Biosintetica (Brazil)	
Modified erythropoietin-α Darbepoietin	Aranesp	Amgen	USA	Amgen	USA, Europe
Modified erythropoietin-α Darbepoietin	Nespo	Amgen		Dompé Biotec S.p.A.	Europe
Modified Erythropoietin-β Continuous Erythropoietin Receptor Activator (Pegylation)	Mircera	Roche			Under development

B. Disease Summary

Anemia occurs with varying degrees of frequency and severity in cancer. It is most frequent in genitourinary, gynecologic, lung, and hematologic malignancies (Barrett-Lee 2006, Groopman 1999, Ludwig 2004, Moullet 1998, Tas 2002). Anemia may be directly related to cancer (type, stage) or to its treatment (type, dose). Co-morbid conditions as well as age can aggravate the anemia (Lipschitz 1995).

Oncologic anemia occurs by a variety of mechanisms (Birgegard 2005, Mercadante 2000). Poor oral intake or altered metabolism may reduce nutrients (folate, iron, vitamin B-12) essential for the proliferation and differentiation of erythroid progenitor cells (Borelli 2007). Antibodies in chronic lymphocytic leukemia (CLL), lymphoma, and some solid tumors may cause increased erythrocyte destruction through hemolysis (Rytting 1996). Tumors may cause blood loss via tissue invasion, e.g. gastrointestinal bleeding from colon cancer. Other neoplasms, particularly hematologic malignancies (leukemia, lymphoma, multiple myeloma) can invade the bone marrow and disrupt the erythropoietic microenvironment (Munker 1995, Skilling 1995). In more advanced cases, there is marrow replacement with tumor or amyloid. Marrow dysfunction can occur, however, even in the absence of frank invasion (Faquin 1992, Mikami 1998). Inflammatory cytokines from interactions between the immune system and tumor cells are thought to cause inappropriately low erythropoietin production and poor iron utilization as well as a direct suppression of erythroid progenitor proliferation (Faquin 1992, Miller 1990, Spivak 2002, Ward 1971).

The treatment of cancer may also cause anemia (Barrett-Lee 2000, 2006, Coiffier 2001, Harrison 2000, Ludwig 2004, Skilling 1999). Radical cancer surgery can result in acute blood loss. Radiotherapy and many cytotoxic chemotherapeutic agents cause marrow suppression to some degree. Damage is due to a variety of mechanisms. For example, alkylating agents cause cumulative DNA damage, anti-metabolites damage DNA indirectly, and platinum-containing agents appear to damage erythropoietin-producing renal tubule cells (Girdwood 1976, Horiguchi 2000).

The level at which anemia requires intervention is not well established. By tradition, patients have been transfused at the hemoglobin level of 7 or 8 g/dl to avoid symptoms and physiologic complications. A transfusion of 2 or more units would result in an increase of at least 2 g/dl of hemoglobin (6 units of hematocrit). Indeed, one of the endpoints for pharmaceutical registration, "need for transfusion", employed an 8% hemoglobin cut-off (FDA Medical Officer Review, Aranesp 2002). Most of these practices, however, are based on empiric observations and not clinical trials. In one of the few studies, Carson et al. found that hip-fracture patients transfused to hemoglobin levels in excess of 10 g/dl did not have more exercise tolerance than non-transfused patients who were transfused after hemoglobin levels dropped to below 8 g/dl or patients became symptomatic (Carson 1998).

The British Blood Transfusion Society has delineated the weaknesses in our knowledge base (Murphy 2001). Their guidelines state that transfusions are indicated in patients with hemoglobin levels less than 7 g/dl and that transfusion should not be undertaken for hemoglobin levels greater than 10 g/dl. They indicate that management of patients with hemoglobin levels between 7 and 10 remains unclear although the hemoglobin threshold for the treatment of patients with co-morbid conditions with probably higher than 7 g/dl. The College of American Pathologists (CAP) no longer issues transfusion practice guidelines although they have done so in the past (CAP 2002).

Other groups have developed definitions for anemia and have been cited for these definitions, but these definitions cannot be extrapolated into guidelines for oncologic treatment. The World Health Organization (WHO) definitions for anemia were developed for surveillance of anemia due to nutritional deficiency and parasitic infections (WHO 1994, 2001). The National Cancer Institute (NCI) has information on anemia, but does not issue treatment guidelines (Robin Bason 301-594-9051; NCI anemia information from web). Both the NCI and WHO consider hemoglobin levels less than 6.5 g/dl to be life-threatening.

III. History of Medicare Coverage

Prior to this National Coverage Analysis, there was no National Coverage Decision (NCD) concerning the use of ESAs for the indications discussed in this Proposed Decision Memorandum. Currently, Medicare payment for ESAs for end-stage renal disease (ESRD) related anemia is outlined in the Medicare Benefit Policy Manual, Chapter 15, Section 50.5.2. For other indications, Medicare coverage of ESAs administered incident to a physician service for other indications under Part B is determined by local Medicare contractors.

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage. ESAs fall within the benefits categories specified in 1861(s)(2)(A) & 1861(s)(2)(B) of the Social Security Act.

IV. Timeline of Recent Activities

March 14, 2007
CMS opened an internally generated National Coverage Decision (NCD) to to evaluate coverage of uses of ESAs in non-renal disease applications.

The initial 30-day comment period began.

April 13, 2007
The public comment period closed; 69 timely comments were received.

V. FDA Status

A. Erythropoietin-alpha was the first ESA approved by the FDA for use in renal failure (1989). Subsequently 2 ESAs were approved for the management of the anemia of cancer treatment (chemotherapy) of non-myeloid neoplastic disease: erythropoietin (1993) and darbepoietin (2002).

B. The FDA reviewed results of the Breast Cancer Erythropoietin Trial (BEST) and Henke studies. Concerns regarding an increased rate of tumor progression and increased mortality were incorporated into the Precautions Section of product labeling in 2004.

C. The FDA convened a meeting of the Oncologic Drugs Advisory Committee 5/4/2004 to discuss safety issue for ESAs. The briefing information and transcript for the meeting is available at www.fda.gov/ohrms/dockets/ac/cder04.html#Oncologic.

D. In conjunction with the FDA, Amgen issued a "Dear Doctor Letter" regarding the use of ESAs for anemia management in the absence of chemotherapy was sent 1/26/2007. (See www.fda.gov/medwatch/safety/2007/safety07.htm#Aranesp)

E. Serial FDA ALERTS regarding ESA safety information were issued: 11/16/2006, 2/16/2007, and 3/09/2007.

F. The FDA strengthened its warning about cardiovascular and thrombotic events in a variety of populations via a BLACK BOX warning. The FDA included BLACK BOX warnings for tumor progression and decreased survival in cancer patients undergoing cancer treatment. The FDA also warned that ESAs are not indicated for anemic cancer patients not undergoing treatment and that mortality is increased when ESAs are used by this population. Specific warnings on the use of ESAs included that they:

- shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a hemoglobin of greater than 12 g/dL,
- shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL,
- increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population.

VI. General Methodologic Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. Critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that are used to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, the blinding of readers of the index test and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

We are providing a summary of the evidence that we considered during our review. We will, of course, consider additional evidence submitted through the public comment period.

Emerging data suggest that ESAs are associated with increased mortality and morbidity despite the alleviation of anemia. The evidence reviewed in this NCA includes the literature on ESA therapy in cancer and focuses on the safety considerations. Most of the studies address the use of ESAs for the treatment or prophylactic management of cancer therapy-related anemia. Select studies address the use of ESAs to treat tissue hypoxia in cancer and thereby attempt to improve response to cancer treatment. Still other studies addressed the use of ESAs in cancer patients without clinically significant anemia. Because of the nature of the findings, literature sources other than the standard medical journals were used when necessary.

B. Discussion of evidence reviewed

1. Questions

1. Is the evidence sufficient to conclude that erythropoiesis stimulating agent (ESA) therapy affects health outcomes when used by Medicare beneficiaries with cancer and related neoplastic conditions?

2. If the answer to Question 1 is affirmative, what characteristics of the patient, the disease, or the treatment regimen reliably predict a favorable or unfavorable health outcome?

Outcomes

We preface our consideration of the questions with a discussion of the evidence regarding appropriate outcomes (endpoints) for trials of ESA treatment. Because of concern about serious adverse effects including death, we are focusing on evidence of morbidity and mortality. Most trials have enrolled subjects with a variety of underlying diseases, especially in the trials of cancer where multiple cancer types are represented by the subjects. In light of evidence that the ESA effect may vary by cancer type, it is possible that trials may dilute and thereby underestimate the effect of ESA usage in some cancers.

We are concerned that a number of trials have been terminated, suspended, or otherwise not completed, possibly due to signals of harm, and that the existing fund of published evidence may reflect a bias toward ESA use. For example, the Securities and Exchange Commission (Atlanta bureau) is reported to be investigating Amgen for failure to disclose to investors until 2/2007 that a Danish study of darbepoietin use in head-and-neck cancer was terminated in 10/2006 for safety reasons. The SEC request was disclosed in the annual report recently filed with the Agency (NY Times 3/1/07; USA Today 3/11/07).

CMS, as a public health agency, is aware that many clinical trials are statistically powered for efficacy and not for safety. The absence of adverse events in a setting of potential harm with an absence of adequate safety data cannot be interpreted as proof of no harm.

ESA use may impact a beneficiary in many ways. Thus, we believe that the broad questions above are appropriately addressed by reviewing the evidence for the following questions:

1. Do ESAs (individually or as a class) cause morbidity and mortality?
2. Do ESAs contribute to morbidity and mortality?
3. Are morbidity and mortality related to baseline hemoglobin/hematocrit levels, achieved hemoglobin/hematocrit levels, rate of change in hemoglobin/hematocrit levels, dose levels, or stratified hematologic response to dosages?
4. Are morbidity and mortality with ESAs associated with certain cancers?
5. Do ESAs negatively interact with certain cancer treatments?
6. Do comorbidities common in the Medicare population, such as ischemic disease and congestive heart failure, contribute to this putative morbidity and mortality?

2. External Technology Assessments

We are aware of several external assessments of ESAs and describe them below briefly.

National Institute for Health and Clinical Excellence (NICE)

In 3/2006, the National Institute for Health and Clinical Excellence in the United Kingdom issued a final appraisal determination for “Erythropoietin for Anemia Induced by Cancer Therapy” (Nice, 2006). This was followed by an Appeals Panel that convened in 6/2006 (Nice, 2006 B). The Cochrane Collaboration, an independent, international, not-for-profit organization that prepares and disseminates systematic reviews of healthcare interventions and promotes the search for evidence, prepared an analysis for NICE (Bohlius, 2007). NICE concluded that “Erythropoietin is recommended for use in the management of anaemia only as part of ongoing or new clinical trials that are constructed to generate robust and relevant data in order to address the gaps in the currently available evidence as outlined in Section 5.” Research is needed to confirm the benefits and risks associated with erythropoietin in the management of anaemia induced by cancer treatment (specifically mortality benefits and risks) and to identify patient subgroups (including those with different tumour types) in whom the possible risks are acceptable.”

Cochrane Collaboration

(See above.)

Agency for Healthcare Research and Quality (AHRQ)

The AHRQ analysis was structured to assess comparative efficacy for the two FDA approved ESAs, erythropoietin and darbepoetin (BC-BS contract #29020026). The authors concluded that there were not definitive data to indicate that ESA use improved tumor response to treatment and that enhancement of tumor progression was uncertain. The authors indicated that none of the studies, including the unpublished work presented by pharmaceutical sponsors at the 2004 ODAC meeting were designed to test survival.

3. Internal Technology Assessment

Systematic reviews are based on a comprehensive search of published materials to answer a clearly defined and specific set of clinical questions. A well-defined strategy or protocol (established before the results of individual studies are known) is optimal.

CMS staff extensively searched Medline (1988 to present) for primary studies evaluating ESA therapy in cancer. The emphasis was on studies structured to assess adverse events and mortality. CMS staff likewise searched the Cochrane collection, National Institute for Health and Clinical Excellence (UK) appraisals, and the Agency for Healthcare Research and Quality library for systematic reviews and technology assessments. Systematic reviews were used to help locate some of the more obscure publications and abstracts. Preference was given to English publications.

Because much of the material remains outside the domain of the published medical literature, additional sources were used. CMS examined FDA reviews of the registration trials for erythropoietin and darbepoetin as well as the FDA safety data for erythropoietin and darbepoetin. CMS reviewed the transcripts and briefing documents (FDA and pharmaceutical sponsor) from the 2004 FDA Oncologic Drug Advisory Committee meeting on ESA safety. CMS reviewed the FDA ESA drug safety alerts and label changes. CMS searched the National Institutes of Health Clinical Trials.gov database for ongoing/completed trials of ESAs. CMS used internet searches to identify websites with clinical trial results, press releases for clinical trial termination, and U.S. government regulatory action.

Keywords used in the searches included: erythropoietin and survival, darbepoietin and survival, epoetin and survival, erythropoietin and mortality, darbepoietin and mortality, epoetin and mortality, erythropoietin and thrombosis, darbepoietin and thrombosis, epoetin and thrombosis, erythropoietin and tumor progression, darbepoietin and tumor progression, epoetin and tumor progression, erythropoietin and cardiovascular, darbepoietin and cardiovascular, and epoetin and cardiovascular.

Despite an exhaustive search, we identified no high quality, randomized clinical trials that were of sufficient duration and powered to definitely determine the risk of adverse events including death, tumor progression, and cardiovascular-thromboembolic events in cancer patients, particularly geriatric cancer patients, using ESAs. No trials were structured to assess these hard endpoints in patients with different cancers, cancers at various stages, cancers treated with different modalities or drugs, variable ESA dose responses, and variable comorbidities. We did identify one high quality published trial that was structured to assess locoregional progression (Henke 2003). It did adjust for baseline tumor stage, but was not powered to assess risk for the various tumor stages. Also, in this study, erythropoietin was employed to putatively enhance radiotherapy through a reduction in hypoxia and not to just alleviate anemia. We did identify multiple studies that were terminated for safety reasons. Most of these were never published as full-length articles in Medline journals.

A. Registration Trials

The clinical trials of ESAs that were submitted for FDA approval (registration) were of relatively short duration (12-16 weeks) and focused on non-survival endpoints, specifically reduction of the need for transfusion, change in hemoglobin, and quality-of-life. [Table 2A and 2B in Appendix B]. Many were very small and assessed heterogenous patient populations, primarily those with solid tumors. Indeed the initial erythropoietin approval was based on a composite of 72 non-platinum chemotherapy treated patients from 3 studies and a composite of 59 platinum chemotherapy treated patients from 3 studies in which the primary endpoint, transfusions, was not attained. In a post hoc analysis, transfusions were reduced during the 2nd and 3rd months of treatment. Furthermore, the data from the most extensive blinded, placebo controlled studies of lymphoproliferative disease (darbepoetin #20000161) submitted to the FDA was not included in the FDA label. In addition, the inclusion critieria for most studies included an expected lifespan of at least 3-6 months or an Eastern Cooperative Oncology Group (ECOG) performance score of 2 or less (ECOG website, Aranesp Medical Officer Review 2002, 2006, Procrit 1993 FDA Summary basis of approval, Procrit 2004 Medical Officer Review). Significant cardiac disease and hypertension were generally excluded. As such, these studies were not structured to assess mortality and more chronic morbidity. Of note, however, a FDA integrated summary of safety for darbepoetin performed with pooled data from 7 studies suggested that fluid overload is more common in oncologic patients on either darbepoetin (n=975) or erythropoietin (n=115) than placebo (n=221) and that a rapid rise in hemoglobin may be associated with fluid overload, hypertension, and thrombosis.

B. Early Promising Studies

Three early studies by Glaser et al. and Littlewood et al. and Antonadou et al. suggested that ESA therapy might contribute to improved survival and tumor control (Antonadou et al., Glaser 2001, Littlewood 2001). The first was a retrospective review of a small population (n=191) of head-and-neck cancer patients who underwent surgical resection after external beam radiation and adjuvant chemotherapy (mitomycin and 5-flourouracil) (Glaser 2001). Patients were stratified by tumor stage, baseline hemoglobin, and use of erythropoietin. A pre-treatment hemoglobin level of 14 g/dl or greater portended a better prognosis than lower levels. Patients with hemoglobin levels under 14.5 g/dl who were treated with erythropoietin (150 U/kg TIW) had greater likelihood of survival (50/57) than those who did not receive erythropoietin (52/87; p=0.001). Loco-regional control was also better (p=0.001). This study was complicated by the lack of randomization.

The second study was a prospective, blinded study in 375 patients with a variety of cancers who were randomized to erythropoietin (150 U/kg TIW) or placebo for up to 28 weeks (Littlewood 2001). The dose could be doubled in poor responders. The primary endpoint was the fraction of patients who received transfusions after 4 weeks of ESA treatment. The study was later amended to include survival. The follow-up period was 12 months after the last patient completed the study. There was a trend towards improved survival in the erythropoietin group: 37% vs 33%; p=0.13. The median survival was 17 months in the erythropoietin group vs 11 months in the placebo group. The study was complicated by a high drop-out rate (159 of 375), the absence of a treatment protocol for patients with iron deficiency, variable doses, variable duration of follow-up, and the admixture of tumors. The solid tumors were comprised primary of breast and gastrointestinal tumors whereas the hematologic tumors included chronic lymphocytic leukemia, non-Hodgkin’s lymphoma, Hodgkin’s lymphoma, and multiple myeloma. Survival was greater in patients with hematologic cancers.

The third study was a prospective study in 385 patients with pelvic malignancies treated with radiation (Antonadou 2001). Patients were randomized to erythropoietin or placebo. The primary endpoints were changes in hemoglobin and local tumor control. The secondary endpoints included disease-free survival and overall survival. Reportedly disease-free survival at 4 years was better in the erythropoietin group. Unfortunately, this study has only been published as an abstract despite its completion in 2000 or 2001. As such there are many outstanding questions about the study's design, e.g., inclusion-exclusion criteria, blind status, drug dose escalation, stratification by disease and stage, treatment duration, follow-up strategy, power calculations, and statistical plan, as well as study results, e.g. baseline characteristics, drop-out rate, and intent-to-treat analyses.

A fourth study, by Vansteenkiste et al., was constructed to assess a 50% reduction in the proportion of patients with at least 1 transfusion during week 5 until the end of the 12 week double-blind, placebo-controlled, treatment phase in anemic patients (hemoglobin ≤ 11 g/dl) randomized to darbepoetin (2.25 mcg/kg/wk initial dose; 4.5 mcg/kg/wk in poor responders) or placebo (Vansteenkiste 2002). Patients were followed for another 4 weeks and then for another unspecified duration. The manuscript reports that survival and tumor progression did not differ by treatment cohort as of 8/2001, a mean duration of follow-up of 1 year. Criteria for follow-up and drop-out rates during this phase of the trial were not reported. Publications of future planned analyses could not be located.

C. Other Published Trials

More than 100 papers on ESA use in cancer and related disorders have been published. Most studies have not been structured to assess survival, tumor progression, and adverse events. Many studies enrolled patients with a variety of tumors. Others enrolled patients with a variety of tumor stages. Many studies included patients on a variety of chemotherapy or radiation treatment regimens. Many of the studies were not randomized, double-blind placebo controlled trials. Active control with another ESA was common. Most studies did not employ fixed ESA doses; instead doses could be titrated upwards in poor responders. Concomitant iron administration was sometimes limited to patients in the ESA cohort. Study endpoints were generally hemoglobin thresholds, changes in hemoglobin, transfusion requirements (without a protocol defining transfusion requirement), or quality-of-life. Many studies did not declare a primary endpoint. Survival and/or tumor progression were secondary or add-on endpoints. No studies presented *a priori* power calculations for the numbers of patients and the study duration required to show a clinically significant survival difference for the specified neoplastic disease. No studies presented *a priori* methods for assessment of tumor progression. Any putative risk was presumed not to vary by tumor type or stage, treatment modality, ESA dose, or ESA response to dose. (See Table 3 in Appendix)

D. Terminated Trials

Emerging data suggest that ESA use may be associated with increased morbidity and mortality. The events are not limited to any single pharmacologic agent, to any specific tumor, or to concomitant use with any single therapeutic regimen (Table 4). Complete data from these studies are lacking. Several of these studies were initiated in response to phase 4 commitments to the FDA because of concerns about tumor progression and mortality. Available data are delineated below.

Table 4: Terminated Trials

Cancer Tx	Cancer	Drug	Investigator/Study #/Author	Complete Published Study
Chemotherapy	Lung (non-small cell)	Pegylated Epo β	Unknown	No
	Lung (small cell)	Epo α	Vercammen in J&J briefing document N93-004 Grote published 2003 abstract & 2005 paper	Yes, under Grote et al.
	Breast	Epo α	Leyland-Jones	Yes, letter 2005 article 2005
	Breast	Epo α	Rosenzweig	Yes, 2004
Immunotherapy	Colon	Darbe α	Unknown	No
Radiotherapy	Head-neck	Darbe α	Danish Head & Neck Cancer 10 Study Group	No
	Head-neck	Epo α	Machtay	No
	Head-neck	Epo β	Henke	Yes, 2003

Cancer Tx	Cancer	Drug	Investigator/Study #/Author	Complete Published Study
	Head-neck	Epo α	Johnson & Johnson EPO-GBR-7	No Reportedly terminated bc of slow enrollment at 301 of 800 in 2002. 5 yr f/u pending.
Chemo-Radiotherapy	Gastric/Rectal	Epo α	Vadhan-Raj PR00or1-03-006	No
	Cervical	Epo α	Unspecified investigators for investigator initiated protocol Johnson & Johnson PR01-04-005/GOG-0191	No
	Lung (small cell)	Epo α	Wright Johnson & Johnson EPO-CAN-15	Yes, 2007
None	Lung (non-small cell)	Epo α	Unknown	No
None	Assorted	Darbe	Unknown	No

Tx= treatment Epo= erythropoietin Darb= darbepoetin bc= because fu= follow-up

<u>Non-small Cell Lung Cancer, Receiving Chemotherapy, Pegylated Erythropoietin β</u>
(Hoffmann-LaRoche Funding) (FDA Alert)

A prospective, 4-arm, dose-finding trial was conducted in anemic Stage III or IV non-small cell lung cancer patients undergoing first-line chemotherapy. Pegylated erythropoietin was titrated to achieve hemoglobin levels between 11 and 13 g/dl. The study was terminated after enrollment of 153 patients because of increased mortality in the experimental treatment arms.

Breast Cancer, Receiving Chemotherapy, Erythropoietin α
(Ortho Biotech/Johnson & Johnson Funding)

(Published letter and paper- Leyland-Jones 2003 and 2005) (FDA review-2004)

This prospective, placebo-controlled, randomized, non-U.S. study (Breast Cancer Erythropoietin Trial [BEST] [EPO-INT-76]) (n=939) in minimally anemic (hemoglobin $\leq$ 13 g/dl) metastatic breast cancer patients, who were on first line chemotherapy/hormone (but not homogeneous) therapy and whose disease was stratified for metastasis location, was structured for survival analysis. These patients with ECOG scores $\leq$ 2 received erythropoietin (40,000-60,000 U/week) or placebo for 12 to 24 weeks to achieve target hemoglobin levels 12-14 g/dl (Oken 1982). Enrollment began in 2000. The treatment arms were well balanced with regard to baseline demographic features, tumor-related characteristics, and hematologic values. (Only 21% of the study population was 66 or older; 4% 76 or older, and 2% from minority groups.) A data safety monitoring board was instituted 1/2002 at the behest of German and British ethics committees. An unplanned interim analysis and eventually trial termination resulted. 59% of hemoglobin values in erythropoietin treated patients were within target vs 45% in placebo treated patients. The erythropoietin cohort experience decreased survival at 12 months: 70% vs 76% (p= 0.012) (Table 5). The increased mortality occurred primarily during the first 4 months. Most of the early deaths were attributable to early disease progression: 6% vs 3%. Others were attributable to vascular and thrombotic events: 1% vs 0.2%. Persistently low hemoglobin levels portended reduced survival regardless of treatment cohort. Reportedly, an analysis of cardiovascular/thrombotic events and absolute hemoglobin levels could not be undertaken because of insufficient data. The principal investigator criticized the study for its inability to collect data on potential prognostic variables (Leyland-Jones 2003). More complete study results were published in 2005 (Leyland-Jones 2005). Its results prompted the FDA 2004 ODAC meeting.

Table 5: Death Profile in BEST

	Erythropoietin α (n=469)		**Placebo (n=470)**	
	4 months	12 months	4 months	12 months
Died	41	148	16	115

	Erythropoietin α (n=469)		Placebo (n=470)	
Disease Progression	28	126	13	105
Thrombotic/Vascular Event	5	6	1	3
Chemo Toxicity	NA	8	NA	1

Breast Cancer, Receiving Chemotherapy, Erythropoietin α
(*Ortho Biotech/Johnson & Johnson Funding) (Published article-Rosenzweig et al. 2004)*

Mildly anemic (hemoglobin <12 g/dl) metastatic breast cancer patients were randomized to usual care or usual care plus open-label subcutaneous erythropoietin for a 12 week study. The initial dosing was 40,000 U per week. At week 4, if the hemoglobin had not increased by at least 1 g/dl, the dose was increased by 50%. If patients continued to be unresponsive to erythropoietin at week 8, the drug was discontinued. The trial was terminated by the investigators after recruitment of only 27 patients when 4 thrombotic events (deep vein thrombosis, pulmonary embolism with deep vein thrombosis, pulmonary embolism with deep vein thrombosis 1 month after drug discontinuation, and brachial vein thrombosis with an infected Mediport) occurred in the experimental arm. In addition, hypertension contributed to the discontinuation by 1 patient in the erythropoietin cohort. Disease progression was similar for the 2 treatment arms (Rosenzweig 2004).

Colon Cancer, Receiving Immunotherapy, Darbepoietin α
(Amgen Funding) (Press release)

Colon cancer patients treated with Vectibix (panitumumab, the human monoclonal antibody directed against epidermal growth factor receptor) (but not chemotherapy or radiotherapy) and darbepoetin-alfa) experienced decreased survival within 16 weeks. The need for transfusion did not differ between those who received darbepoietin and those who did not.

Head-and-neck Cancer, Receiving Radiotherapy, Darbepoietin α
(Amgen Funding)
(Danish Head and Neck Cancer Group website publication:conman.au.dk/dahanca)

Advanced stage head-neck cancer patients treated with radiotherapy and randomized to open-label darbepoietin (vs placebo) in the Danish Head and Neck Cancer 10 Study (N=600 planned, 522 randomized, 516 eligible, 484 with sufficient study time for interim analysis) experienced worse clinical outcomes despite target hemoglobin levels of 14.0 to 15.5 g/dl during radiation therapy. Loco-regional disease progression was greater at 3 years (p=0.01). Overall mortality also tended to be greater (p=0.08). The findings were thought to be significant enough to result in trial termination. Studies on erythropoietin receptor tissues numbers will be undertaken 5/2007. It should be noted that this study was conducted to fulfill a phase 4 commitment to the FDA for the study of tumor progression and survival. Before the trial was terminated, a report to the FDA was originally due 9/2008.

Head-and-neck Cancer, Receiving Radiotherapy, Erythropoietin α
Drug supplied by Ortho Biotech)
(Non-Medline published abstract-Machtay et al. 2004; RTOG 99-03 website)

The study was an international, prospective, randomized, phase III NCI study (PR99-03-046) to assess the role of erythropoietin (40,000 U/wk SQ x 8-9 weeks) in anemic patients (hemoglobin <12.5 g/dl in women and ,13.5 g/dl in men) with Stage I-IV head-and-neck cancer treated with radiotherapy. The hypothesis was that reduction of hypoxia with an erythrocyte stimulating agent would enhance radiosensitivity. Concomitant platin therapy was not mandated, but permitted. The endpoint was death or local-regional failure (persistent or recurrent disease in the primary tumor or regional nodes). An interim analysis was prompted by the Henke study (Henke 2003). There was a trend towards a less favorable outcome in patients in the erythropoietin arm, but statistical significance was not reached. The investigators, the Radiation Therapy Oncology Group, suspended study enrollment in 11/2003 after entering 148 of 372 planned patients. Erythropoietin dosing was immediately discontinued. The investigators recognized the statistical power losses introduced by the early termination.

Head-and-neck Cancer, Receiving Radiotherapy, Erythropoietin β
(Hoffman LaRoche Funding) (Published article- Henke et al. 2003)

Three hundred fifty-one advanced head-neck squamous cell cancer patients with mild anemia (hemoglobin <12 g/dl [women]; <13 g/dl [men]) were randomized to erythropoietin-beta (300 U/kg TIW) or placebo prior to and during radiotherapy (60 or 70 Gy) in a prospective, blinded, randomized, placebo controlled study (MF-4449; ENHANCE) (n=351) by Henke et al. The erythropoietin group experienced more local progression over time (relative risk: 1.69; p=0.007) and reduced survival (relative risk: 1.39; p=0.02) than those who did not receive erythropoietin. This pattern was present regardless of tumor resection status, and occurred despite anemia correction. Eighty-two percent of patients on erythropoietin vs only 26% of patients on placebo achieved hemoglobin levels >15 g/dl (men) or >14 g/dl (women). Prognosis was in part related to hemoglobin concentration at baseline and response to fixed dose therapy, i.e., 300 u/kg/TIW during radiation. Patients on erythropoietin also appear to experience more vascular disorders (hypertension, hemorrhage, venous thrombosis and pulmonary embolism, and cerebrovascular disease) (11% vs 5%). Of the 15 cardiac deaths, 10 occurred in the erythropoietin treatment arm.

Gastric/Rectal Cancer, Receiving Chemo-radiotherapy then Surgery, Erythropoeitin α
(Johnson & Johnson Funding)
(Published Non-Medline Abstract-Vadhan-Raj et al. 2004)

(Johnson & Johnson FDA briefing document)

Patients with rectal or gastric cancer with hemoglobin levels 10 to <15 g/dl were randomized to erythropoietin 40,000 U/wk or placebo in a double-blind, prospective, double-blind study in which patients underwent chemo (fluoropyramide)-radiotherapy prior to surgical resection. If the hemoglobin remained below 13 after 4 weeks, the dose was increased by 50%. The study was terminated because of increased thrombo-embolic-vascular events. Data were reportedly available for 59 of the planned 184 patients. Eleven percent (6/53) of the events occurred in patients with rectal cancer; 33% (2/6) occurred in patients with gastric cancer. Twenty-one percent (6/28) of events (primarily serious deep vein thromboses) occurred in patients on epoetin; 6% (2/31) occurred in patients on placebo. Twenty-one percent (7/35) of patients with hemoglobin levels in excess of 13 g/dl experienced; 4% (1/24) occurred in patients with lower levels. The small numbers preclude more extensive analysis.

<u>Lung Cancer, Receiving Chemo-radiotherapy, Erythropoeitin α</u>
(Johnson & Johnson Funding) (Briefing document for FDA meeting)

This study was a double-blind, randomized, placebo-controlled study (EPO-CAN-15) in which patients with limited small cell lung cancer treated with combined chemo- radiotherapy were randomized 1:1 to erythropoietin (40,000 U/wk). The initial treatment target was hemoglobin levels 14-16 g/dl. This was later lowered to 13-14 g/dl. The study appears to have been terminated following thrombo-embolic-vascular events and related deaths. Data were reportedly available for 106 of the planned 620 patients. Nineteen events occurred in the epoetin arm (albeit 2 prior to treatment); 3 occurred in the placebo arm. Four of the epoetin patients with thrombo-embolic-vascular events died. Fourteen of sixteen patients with thrombo-embolic-vascular events were randomized when the hemoglobin target level was 14-16 g/dl. The small numbers preclude more extensive analysis.

<u>Breast Cancer, Receiving Chemotherapy & Later Radiation, Erythropoietin α</u>
(Ortho Biotech/Johnson & Johnson Funding)
(Published paper- Grote et al. 2005)

A prospective, double-blind trial (N93-004) was conducted in small cell lung cancer patients who were to receive up to 12 cycles of chemotherapy; at least 3 of these being etoposide/cis-platinum. Radiation therapy could be added after the third chemotherapy cycle. Patients were randomized to placebo or erythropoietin α 150 U/kg TIW during and for 3 weeks after the completion of chemotherapy. Because the study was to fulfill a 1993 phase 4 safety commitment to the FDA, patients were to be followed for an additional 3 years. The study was structured as a non-inferiority trial. Tumor responses were categorized as complete remission, partial remission, no response, or disease progression. The study was reportedly terminated at 224 of 400 because of slow enrollment. It should be noted that a divergence in survival, in favor of placebo, could be noted at 16-20 months and persisted. With the truncated enrollment, this finding did not reach statistical significance.

The 2004 ODAC Briefing Document and transpscripts were initially available as an internal pharmacologic industry document: Vercammen E, Sullivan D, Matone P. The effect of r-HuEPO in patients with small cell lung cancer (SCLC): A randomized, double-blind, placebo-controlled trial. Protocol N93-004; Phase 4. Document ID No. EDMS-USRA-8057829:4.0. Sept. 26, 2002. This information was later presented in the 2004 J&J ODAC briefing document and at the meeting (2004 ODAC briefing document & transcript). There was no subsequently published study by this author in Medline (Accessed 4/9/07). There is a publication by Grote et al. that describes this study (Grote 2005).

Non-small Cell Lung Cancer, Not Receiving Chemotherapy, Erythropoietin α
(Funded by Ortho Biotech/Johnson & Johnson Funding)
(Briefing document for FDA meeting) (FDA Alert)

A prospective, double-blind, placebo controlled trial (EPO-CAN-20) was conducted in anemic non-small cell lung cancer patients not undergoing chemotherapy. Erythropoietin was titrated to achieve hemoglobin levels between 12 and 14 g/dl. The endpoint was quality of life. Planned enrollment was 300 patients. Study enrollment was terminated after 70 patients because of increased mortality in the experimental treatment arm. The median time-to-death was shorter in the erythropoietin cohort: 68 days vs 131 days; p=0.04. The increased mortality was attributed primarily to disease progression. Quality of life and the need for transfusion were not better in the erythropoietin arm. Reportedly enrollment was terminated in 12/2003. Preliminary results were included in the briefing document, but apparently FDA was not notified of additional study analyses until 2/2007.

Assorted Cancers, Not Receiving Chemotherapy, Darbepoietin
(Funded by Amgen)
(Press release; American Association for Cancer Research Annual Meeting Webcast)

Patients (N=989) with a variety of active cancers, including hematologic cancers, who were anemic (hemoglobin <11 g/dl), but were not undergoing myelosuppressive chemotherapy or radiotherapy, were randomized to darberpoietin or placebo in a 16 week, double-blind trial with follow-up. Patients were to have a life expectancy greater than 4 months and an ECOG score of 2 or less. There was stratification by entry hemoglobin (<10 g/dl or ≥10 g/dl). The primary endpoint was transfusion rate between weeks 5 to 17. Other endpoints included hemoglobin change and quality of life. The patients receiving darbepoietin did not receive fewer transfusions (18% vs 24%; p=0.15, although reportedly fewer patients on darbepoetin would have met the protocol criteria for transfusions. Patients experienced more mortality (136/515 vs 94/470; p<0.05 CI1.04-1.51). The statistical significance in the preliminary analysis reportedly decreased with adjustments for baseline and prognostic characteristics, but still did not favor the ESA. Subgroup analysis suggested that the results varied by tumor. Reportedly the rate of hemoglobin increase, whether induced by drug or not, did not correlate with survival outcome. Poor response rate may have some predictive value. Thrombotic events were somewhat greater in the darbepoetin group (9.7% vs 7.7%). It should be noted that this study was conducted to fulfill a phase 4 commitment to the FDA for the study of tumor progression and survival. A report to the FDA is due 10/2007.

Cervical Cancer, Receiving Chemotherapy & Radiotherapy, Erythropoeitin α
(Funded by Johnson & Johnson) (Briefing document for FDA meeting)

An open-label randomized study (PR01-04-005/GOG-0191) in which patients with cervical cancer treated with concomitant radiotherapy and cisplatin and with hemoglobin levels <14 g/dl were randomized to receive erythropoietin (40,000 U/wk). The dose was increased 50% in poor responders after 4 weeks. The study appears to have been terminated because of excess numbers of thrombo-embolic-vascular events. Data were reportedly available for 79 of the planned 460 patients. 17% (10/58) of events (primarily venous thromboses) occurred in patients on epoetin; 9% (5/55) occurred in patients on placebo. The small numbers preclude more extensive analysis.

E. Ongoing Studies

We identified 17 reportedly ongoing studies in patients with non-myeloid cell line tumors (16 solid tumors, 1 large B cell lymphoma, 1 chronic lymphocytic leukemia) (Table 5). Despite the antiquated start dates for many of the studies, we were unable to locate Medline publications as of 3/28/07. One study investigator, however, has published a discussion paper on the subject. Several studies were initiated as phase 4 commitments to the FDA. Several studies, but not all, are registered with Clinical Trials.gov.

Table 6: Ongoing Studies

Cancer	Drug	Investigator/Study Name	Outcome	Start Date	Clin Trial #
Breast	Epo α	A Howell	Overall survival	2000	
Breast	Darb α	German Gynecological Oncology Study Group "PREPARE" Study DE-2001-0033	Relapse-free survival	2001 1 published article on cognitive function**	Phase 4 Report to FDA due 11/2007*
Breast	Darb α	West German Study Group DE-2002-0015 ARA-03	Event-free survival (death, relapse, 2nd primary)	2002	Phase 4 Report to FDA due 11/2007*
Breast	Darb α	U Nitz Heinrich-Heine University, Duesseldorf	Disease-free & overall survival at 6 mo to 5 yrs after tx	2004	NCT00309920[a]
Breast	Epo α	Johnson & Johnson	Progression-free survival	2006	NCT00338286[b]
Cervical	Epo α	NCI/NIC of Canada GM Thomas/PS Craighead	Progression-free survival Overall survival	2001 No longer recruiting	NCT00017004[c]
Cervical	Epo	JCA Dimopoulos/ Richard Poetter	Remission rate Local control Disease-free survival	2000 Expected completion 2008	NCT00348738[d]
Cervical	Epo α	Blohmer AGO/NOGGO	Relapse-free survival 5 yrs	1999 Abstract published at 2 yrs #	

Cancer	Drug	Investigator/Study Name	Outcome	Start Date	Clin Trial #
Cervical	Epo β	H Koelbl AGO Ovarian Cancer Study Group	Tumor response	2002 (Reportedly still recruiting)	NCT00046969[e]
Head-neck	Epo	P Lambin EORTC 229996-24002	Loco-regional control Overall survival	1999	
Head-neck	Epo α	JS Stewart	Local tumor control Disease-free survival Overall survival	1999	
Head-neck LOOK	Epo α	Cross Canada Institute Parliament	Local tumor control Overall survival	Not known	
Lung	Epo α	M O'Brien	Response to chemotherapy	1998	
Lung (non-small cell)	Epo	AR Blackstock	Tumor response rate Overall survival	2002	
Lung (small cell)	Darb α	Amgen 20010145	Survival time	2002 No longer recruiting	NCT00119613 [f]
Pelvic	Epo α	D Antonadou	Disease-free survival	Not known # #	
Leukemia (chronic lymphocytic)	Darb α	M Hallek German CLL Study Group	Multiple endpoints including survival	2004	NCT00281892[g]
Lymphoma (large B-cell)	Darb α	A Bosley/R Delarue Group d'Etude des Lymphomes de l'Adulte FR-2003-3005 GELA LNH03-6B	Event-free survival	2003 Expected completion 2008	Phase 4 Due 8/1010* NCT00144755[h]

*It should be noted that this study is being conducted to fulfill a phase 4 commitment to the FDA for the study of tumor progression and survival
**Hermelink K, Untch M, Lux MP, Kreienberg R, Beck T, Bauerfeind I, Munzel K. Cognitive function during neoadjuvant chemotherapy for breast cancer: results of a prospective, multicenter, longitudinal study. Cancer. 2007;March 9 E-pub.
***www.fda.gov/ohrms/dockets/AC/04/briefing/4037B2_01_Amgen-Aranesp.doc
Blohmer J, et al. Impact of epoetin alpha on disease-free survival in high risk cervical cancer patients receiving sequential adjuvant chemotherapy. ECCO abstract Sept 2003. GET Nothing on Medline since 4/9/07
Antonadou 2001 abstract
awww.clinicaltrials.gov/ct/show/NCT00309920
bwww.clinicaltrials.gov/ct/show/NCT00338286
cwww.clinicaltrials.gov/ct/show/NCT00017004
dwww.clinicaltrials.gov/ct/show/NCT00348738
ewww.clinicaltrials.gov/ct/show/NCT00046969
fwww.clinicaltrials.gov/ct/show/NCT00119613
gwww.clinicaltrials.gov/ct/show/NCT00281892
hwww.clinicaltrials.gov/ct/show/NCT00144755

4. Medicare Evidence Development and Coverage Advisory Committee (MEDCAC)

A MEDCAC meeting was not convened for this issue.

5. Evidence Based Guidelines/Professional Society Position Published Statements

a. American Society of Hematology (ASH)
Guidelines for ESA use in cancer patients were issued in conjunction with the American Society for Clinical Oncology. They are available as a 2002 publication by Rizzo et al. (Rizzo 2002). The Society has indicated that "Since the publication of this guideline, the product labeling for erythropoiesis stimulating agents has been significantly revised based on emerging safety data." The Society directs site users to the 3/9/ 2007 FDA alert via a web link.

b. American Society for Clinical Oncology (ASCO)
Guidelines for ESA use in cancer patients were issued in conjunction with the American Society of Hematology. They are available as a 2002 publication by Rizzo et al. via request from the Society (Rizzo 2002). The Society has indicated that "Since the publication of this guideline, the product labeling for erythropoiesis stimulating agents has been significantly revised based on emerging safety data." The Society directs website users to the FDA website.

c. National Comprehensive Cancer Network (NCCN)
The National Comprehensive Cancer Network issued updated guidelines from 2/2006 in 1/2007 and 2/2007. Additional revisions are underway. Identification of non-cancer related causes of anemia and appropriate treatment is promoted. It states that cancer-related fatigue is multifactorial, that anemia is only one of the causes, and that this is an active area of investigation. It states that the relationship between anemia and treatment outcome is poorly characterized. It recommends assessment of clinical risk before initiating treatment and determining treatment targets. It acknowledges that "high risk" patients are poorly characterized and that there is a paucity of prospective data regarding their management. It encourages ESA discontinuation in poor responders and dose lowering in brisk responders. Most recently, it has strengthened its warnings about ESA-associated thrombosis based on the meta-analysis by Bohlius et al. and noted the paper's identification of a trend towards reduced survival (Bohlius 2006). It also recommended that physicians not use ESAs in cancer patients with anemia not due to concurrent chemotherapy if the patients are similar to those enrolled in the Amgen trial. The NCCN "believes that the best management of any patient is in a clinical trial. Participation in clinical trials is especially encouraged."

d. European Organization for Research and Treatment of Cancer (EORTC)
The European Organisation for Research and Treatment of Cancer last prepared an update for ESA use in 2006 prior to the emergence of new data (Bokemeyer 2006/7).

"The addition of further level I studies confirms our recommendation that, in cancer patients receiving chemotherapy and/or radiotherapy, treatment with erythropoietic proteins should be initiated at a hemoglobin level of 9-11 g/dl based on anemia related symptoms rather than a fixed hemoglobin concentration…"

“We do not recommend the prophylactic use of erythropoietic proteins to prevent anemia in patients undergoing chemotherapy or radiotherapy…”

“There is only indirect evidence that patients with chemotherapy-induced anaemia or anaemia of chronic disease initially classified as non-responders to standard doses proceed to respond to treatment following a dose increase. None of the studies addressed the question in a prospective, randomised fashion, and so the Taskforce does not recommend dose escalation as a general approach in all patients who are not responding…”

“This analysis confirms that there are no baseline predictive factors of response to erythropoietic proteins that can be routinely used in clinical practice if functional iron deficiency or vitamin deficiency is ruled out; a low serum erythropoietin (EPO) level (only in haematological malignancies) appears to be the only predictive factor to be verified in Level I studies. Further studies are needed to investigate the value of hepcidin, C-reactive protein, and other measures as predictive factors…”

“There is still insufficient data to determine the effect on survival following treatment with erythropoietic proteins in conjunction with chemotherapy or radiotherapy...”

“Likewise, we found no clear link between erythropoietic therapy and other endpoints such as local tumour control, time to progression, and progression-free survival…”

“There is Level I evidence that the risk of thromboembolic events and hypertension are slightly elevated in patients with chemotherapy-induced anaemia receiving erythropoietic proteins.”

7. Public Comments

We received 66 topical comments during the initial public comment period. Of the public commenters who furnished this information, 37 were from providers, 5 were from caregivers, 1 was from a patient, 13 were from professional organizations, 7 were from patient advocacy groups, 1 was from a national oncology policy consulting group and 2 were from pharmaceutical companies. Two comments regarding the use of ESAs for renal disease and two related to code assignments are included in the 70, both topics are outside the scope of this NCD.

The majority of commenters requested CMS to provide coverage of ESAs for all non-renal FDA approved indications. Several commenter included studies and scientific literature with their comments.

Finally, several commenters requested that CMS delay rendering a proposed decision until after the FDA Oncology Drug Advisory Committee (ODAC) meeting scheduled for May 11, 2007. Commenters suggested that CMS review the literature and data distributed at the ODAC meeting prior to rendering the proposed decision. CMS' final decision will be published after the ODAC meeting. CMS will as usual consider additional timely evidence furnished after the publication of the proposed decision.

8. Expert Opinion

CMS has solicited external expert opinion and anticipates receiving responses before the publication of the final decision memorandum.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act §1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member” (§ 1862(a)(1)(A)). This section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment questions:

1. Is the evidence sufficient to conclude that erythropoiesis stimulating agent (ESA) therapy affects health outcomes when used by Medicare beneficiaries with cancer and related neoplastic conditions?

2. If the answer to Question 1 is affirmative, what characteristics of the patient, the disease, or the treatment regimen reliably predict a favorable or unfavorable health outcome?

In the classic paradigm, physiologic replacement of a missing hormone should result in normalization. Indeed many, albeit not all, patients with end-stage renal disease are deficient in erythropoietin because of damage to the renal parenchyma. Their anemia is secondary to and highly responsive to low doses of ESAs. In the non-classic paradigm, a hormone is used at higher than physiologic levels because of hormone resistance or to supplement endogenous pathways to achieve superphysiologic or accelerated physiologic responses.

Early ESA drug development was based on the classic paradigm of erythropoietin action. The endpoints in the clinical trials were reduction in the transfusion rate, quality of life, absolute hemoglobin level, and change in hemoglobin level. The hemoglobin parameters were surrogate endpoints. Because anemia portended poor clinical outcome (Dunphy 1989, Fein 1995, Obralic 1990, Oehler 1990, Reed 1994), it was hypothesized that reversal of anemia itself would improve long-term clinical status. It was presumed that the primary risk was thrombo-embolic-vascular events, and that these were related to hemoglobin level rather than to drug dose and/or response to drug dose. As such, most of the registration trials for FDA approval were relatively small and conducted in patient heterogeneous populations with a mixture of primarily solid tumors at various stages and undergoing treatment with a variety of regimens. (See tables 2A and 2B.) The relative risks and benefits for patients with lymphoproliferative disease are not addressed in the drug label and anecdotal evidence suggest that ESA use in hematologic disease may increase the risk for transformation to plasma leukemia, increased light chain excretion, and decrease the remission interval (Caillette 1993, Olujohungbe 1996, Rogers 1990). The studies were of relatively short duration (12-16 weeks). In addition, entry criteria excluded patients who were sicker because of their oncologic disease or their co-morbidities. Typically life expectancy was to be at least 6 months and/or an Eastern Cooperative Oncology Group (ECOG) performance score of 2 or lower (Oken 1982; ECOG website). In general, patients with New York Heart Association (NYHA) classifications 3 and 4 were excluded. Geriatric patients constituted a relatively small proportion of patients in the registration trials.

Emerging data suggest that ESA use may be associated with increased morbidity and mortality in a variety of patient populations despite the alleviation of anemia. Although the features and exact mechanisms of the increased mortality require better delineation, both thrombo-embolic-vascular disease and tumor progression appear to be involved.

Indeed thrombosis was observed in the early trials in renal patients (the first approved indication for ESAs (Winearls 1986). It was also observed retrospectively (adjusted odds ratio 15.3) in cervical cancer patients. (Wun 2003) More recently thrombosis was observed in patients who received ESAs for spinal and cardiac surgery (D'Ambra 1997, FDA Alert 2007, Procrit label). These data suggest that the thrombotic phenomenon is related to the pharmacologic agent and cannot be entirely attributed to the underlying disease condition.

Etiologic attribution of thrombotic-vascular disease in oncology and cancer treatment, however, is particularly challenging in the absence of randomized clinical trials stratified for a variety of variables because cancer is a hypercoagulable state (Alacay 2006, Chew 2006, 2007, De Cicco 2004, Grudeva-Popova 2005, Semrad 2007, White 2005). Typically the venous system is involved, but arterial thrombosis does occur. Tumor cells release cysteine proteases that activate coagulation cascade factor X and tissue factor (TF) that activates factor VII (Kakkar1995). Sialic chains on the mucin from adenocarcinomas activate factor X (Donati 1984, Pineo 1973). Cancer cells interacting with monocytes and macrophages induce the release of interleukins (IL)(1,6) and tumor necrosis factor (TNF) (De Cicco 2004, Edwards 1981, Rickles 2001, Schwartz 1981). Furthermore, cancer treatment, including radiotherapy and surgery, can also contribute to thrombosis (Hallahan 1999, Schreiber 1986, Wilson 1987). Growth-factors, high dose fluorouracil, L-asparaginase, mitomycin, platinum compounds, and tamoxifen have all been implicated (Deshmukh 1995, Falanga 2001, Feffer 1989, Fisher 1990, Kuzel 1990, Lee 1999, 2006, Levine 1988, Lipton 1984, Pritchard 1996, Rella 1996, Rivkin 1994, Rogers 1988, Saphner 1991, Weitz 1997). Central line catheter surfaces can activate platelets and factors X and XII (Bern 1990, Bona 1999, De Cicco 124, Lockich 1983, Monreal 1991). Infections of such catheters can result in the release of mucopolysaccharides (gram positive organisms) and endotoxins (gram negative organisms) that activate factor XII, IL-1, TF, and TNF. Venous stasis due to immobility and drug therapy also contributes to thrombosis (De Cicco 2004, Kessler 1989, Levine 1993, Sue-Ling 1986, Walsh 1974).

Several studies in cancer patients were terminated because of thrombo-embolic-vascular events. The FDA has strengthened its warnings for these types of events in the ESA drug labels. The mechanism(s) by which ESAs might cause or aggravate thrombosis are not known. ESA-induced hyperviscosity has been postulated as a cause in patients with high hematocrit levels (Begg 1966; Lage 2002; Turito 1980). Hematocrit elevation, however, cannot be the sole cause of thrombosis because platelet number is increased, function altered, and bleeding time shortened even prior to the erythrocytic rise (Akizawa 1991; Ando 2002; Aranesp™ package insert; Homonchick 2004, Kooistra 1994; Malyszko 1995, 1996; Pirisi 1994; Roger 1993, Sharpe 1994; Stohlawetz 2000). Alterations in other coagulation factors (decreased proteins C and S; increased Factor VIII, thrombin-antithrombin (TAT) III complex, thrombin activatable fibrinolytic inhibitor, and von Willenbrand factor) have been reported (Akizawa 1991; Macdougall 1991, Malyszko-A 1995, Taylor 1992, Tobu 2004). It is known that ESAs cause fluid retention and hypertension (Malyszko –B 1995, Maschio 1995, Roger 1996, Winearls 1986). Both of these can precipitate congestive heart failure and resulting venous stasis. Regardless of the cause(s), only careful prospective trials controlled for the various thrombotic risk factors associated with vascular-thrombotic-embolic disease of cancer will delineate the magnitude of risk attributable to ESAs for the various oncologic populations. Medicare beneficiaries may be at increased risk for such events because of increased cardiovascular disease, increased co-morbidity, and decreased mobility.

At the time of initial drug approvals for cancer-treatment associated anemia, the FDA had concerns about ESA mediated tumor initiation or promotion. The FDA requested post-approval phase 4 commitments in 1993 and 2002 to explore this putative risk promotion because the registration studies were not structured to assess overall survival, cause-specific mortality, cause-specific morbidity, tumor-free survival, and tumor progression. The post approval studies permitted heterogeneous patient populations because it was presumed that the risk benefit ratio would be similar for all tumors at all stages, for all treatment modalities, and in all adult patient populations.

In many of the terminated trials, there was a signal suggesting decreased survival. Attribution for the precise determination of mortality cause was often not done or not done rigorously. Nonetheless, results from studies that attempted to assess cancer disease-free survival or changes in locoregional tumor control, suggest that tumor progression plays a more significant role than vascular-thrombotic events in the apparent decreased survival observed with ESA use for the anemia secondary to cancer chemotherapy, an FDA approved indication. A signal for decreased survival was also observed with ESA use for the anemia of cancer (but no therapy) and to reduce tissue hypoxia during radiation treatments, neither of which are FDA approved indications. These observations have resulted in FDA Black Box warnings.

Tumor progression might occur via a number of avenues. Malignant cells could be transformed, or their milieu enriched. The first mechanistic pathway includes the ability of malignant cells to survive via decreased programmed cell death (apoptosis), the ability to survive through resistance to chemo/immuno/radiotherapy, increased proliferation leading to greater tumor burden, enhanced invasiveness, and improved migratory or metastatic travel capacity. Another mechanistic pathway includes decreased tissue hypoxia and increased nutrient supply via a more extensive vascular network (angiogenesis) and increased erythrocyte number.

There is a significant amount of in vitro work to support the first pathway, and this might inform CMS in its coverage decision in the absence of definitive clinical data (Acs 2001, 2002, 2003; Anagnostou 1990, 1994; Arcasoy 2003, 2005; Batra 2003; D'Andrea 1989; Digicaylioglu 1995; Farrell 2004, Fraser 1989; Haroon 2003; Henke 2006, Jones 1990; Kumar 2006, Lai 2005; Lappin 2003, Masuda 1993; Mioni 1992, Ogilvie 2000, Ribatti 2003; Rossert 2005, Selzer 2000; Westenfelder 2000; Wright 2004; Winkelman 1990 Yasuda 1998, 2001, 2006). Indeed, elements of the erythrocyte receptor signaling cascade are similar to those of epidermal growth factor (EGF) receptor, a target against which immunotherapeutic agents are being developed (Wakao 1997, Zhang 2006). Locoregional progression of head-and-neck cancer was increased in patients with tumors positive for erythropoietin receptors and who were treated with erythropoietin (Henke 2006). There is a trend for such progression even in the patients with erythropoietin receptors who did not receive erythropoietin suggesting that endogenous erythropoietin might be variable and able to impact clinical outcome (Henke 2006). Cultured cells (cervical cancer line HT100 and glioma line U87) developed resistance to ionizing radiation and cis-platinum after exposure to erythropoietin (Belenkov 2004, Yasuda 2003). Incubation with an inhibitor to the erythropoietin receptor's JAK-STAT pathway, typhostin (AG490), could reverse this resistance (Belenkov 2004).

The picture, however, is not straightforward. As such, universal statements about ESA use in oncology cannot be made. Erythropoietin receptor number may change with the cell cycle (Acs 2001, Broudy 1991). The number may increase with the stage of the tumor (Acs 2001). Some cell lines do not exhibit proliferation in response to erythropoietin exposure (Wesphal 2002). Indeed, Henke et al. found that locoregional progression of head-and-neck cancer was not increased in erythropoietin-treated patients lacking erythropoietin receptors (Henke 2006). Mittelmann et al. even found that myeloma regression in mice after ESA treatment (Mittelmann 2001). Tovari et al. found that ESA treatment might enhance sensitivity to 5-fluorouracil chemotherapy (Tovari 2005).

There is also a significant amount of in vitro work that supports the second mechanistic pathway. Microvascular density and tumor stage (for neuroblastomas and hepatocellular carcinomas) have been found to correlate with both erythropoietin and erythropoietin receptor expression (Ribatti 2007 A&B). This suggests that there is tumor secretion of erythropoietin that binds to erythropoietin receptors on vasculature which, in turn, proliferates and further promotes tumor growth (Ribatti 2007 A&B). Secretion of pro-angiogenic factors and recruitment of vascular endothelium has also been observed with human mesenchymal stem cells (which, like cancer cells, are less differentiated than normal cells) (Zwezdaryk 2007). There has even been a report of the conversion of myelodysplastic syndrome (MDS) to leukemia attributed to erythropoietin's angiogenic effects on the bone marrow (Bunworasate 2001, Ribatti 2002). Indeed anti-angiogenic monoclonal antibody therapy has been approved for colon cancer and is under development for other tumors (Panares 2007). Nonetheless, erythropoietin-induced angiogenesis has not been found in all cancers or test models (Hardee 2005).

Oncology patients may be exposed to supraphysiologic ESA doses. Many cancer patients manifest erythropoietin resistance, i.e., they have an inappropriately low endogenous erythropoietin response to anemia (Ward 1977) and do not respond to low exogenous dose levels (Miller 1990). This is likely to be compounded in geriatric patients who are known to have reduced hematopoietic reserve (Miller 1990). Less frequent dosing regimens, although equivalent to more frequent dosing regimens on the basis of a hematologic response, result in higher peak blood levels of hormone (Chung 1998, 2001, Kryzunski 2005, Ramakrishnan, 2004). It is not known whether supraphysiologic ESA blood levels would increase the likelihood of spill-over from the classic high affinity erythropoietin receptor binding sites in the bone marrow to non-marrow receptors with different binding constants where it can act as a growth factor (Fraser 1988, 1989, Masuda 1993, Hardee 2006) or whether excess hormone is bound by the soluble erythropoietin receptors secreted by some tumors (Harris 1996; Maeda 2001, Wesphal 2002).

Regardless of the cause(s), careful prospective trials controlled for the tumor, tumor stage and perhaps tumor cell cycle, cancer treatment, and perhaps endogenous systemic or paracrine/autocrine erythropoietin production and the presence of erythropoietin receptor on tumors and as soluble elements in the blood are needed to inform CMS determinations as to whether ESAs provide a meaningful clinical benefit for the various oncologic populations. Careful trials would also assess the effects of dose including doses in patients who exhibit a poor hematologic response to low doses as well as the effects of long-term dosing and repeated dosing.

Summary

We cannot be sure of the completeness of the evidentiary database because of the question of unpublished data. Negative studies were frequently not available as full published reports on Medline. The early termination of studies by data safety monitoring boards, investigators, and/or pharmaceutical sponsors because of a safety concern does not permit complete appraisal of the magnitude of safety risk. Early termination may reduce the statistical power of a safety finding. Nonetheless, evidence of harm is apparent despite these limitations. ESA treatment is associated with an increased risk of thrombotic-vascular disease, tumor progression, and decreased survival. Furthermore there are potential mechanisms that could explain the etiology of the harm.

Although the data are less robust than we would like, particularly for geriatric patients, they are sufficient to identify patient characteristics and treatment practices that increase the likelihood of unfavorable clinical outcomes. Increased thrombotic-vascular disease, tumor progression, and/or decreased survival occurred with ESA use to prevent or treat anemia secondary to cancer, cancer chemotherapy, or radiotherapy or to improve tissue hypoxia in an attempt to enhance tumor sensitivity to therapy.

From the evidence reviewed, we believe that:

- cancers with erythropoietin receptors-especially when coupled with extensive exogenous ESA exposure may predict increased risk for tumor progression and/or decreased survival.
- the risk:benefit profile is less defined for hematologic cancers because FDA reviewed studies are lacking and patients with myelogenous cancers were excluded from studies.
- a variety of factors including a rapid rise in hemoglobin, a normalized hemoglobin, and a high ESA dose requirement may contribute to or portend increased risk for thrombotic-vascular events
- patients with poorly controlled hypertension, fluid retention, congestive heart failure, and prior thrombo-embolic events are at increased risk for future thrombotic-vascular events with ESA use.
- ESAs may negate the therapeutic utility of anti-angiogenesis and anti-EGF receptor agents.
- bone marrow or progenitor cells within the bone marrow damaged by proliferative or scarring disease have not been adequately shown to respond to low ESA doses without sequelae.

Especially in the setting of potential harm, we believe ESA treatment is not a reasonable substitute for targeted therapy addressing the underlying cause(s) of the anemia. Anemia due to vitamin or mineral deficiency should be addressed by supplementation of those nutritional deficiencies. We believe that ESA use is reasonable and necessary only in clinically significant anemias due to chemotherapy when used at low doses for short durations. In particular, appropriate limitations should be applied to ESA use by beneficiaries with tumors with erythropoietin receptors. ESA use is not reasonable and necessary in beneficiaries with a poor hemoglobin response.

IX. Conclusion

CMS is seeking public comment on our proposed determination that there is sufficient evidence to conclude that erythropoiesis stimulating agent (ESA) treatment is not reasonable and necessary for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on their underlying disease or because the underlying disease increases their risk of adverse effects related to ESA use. These conditions include:

1. any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
2. the anemia of myelodysplasia
3. the anemia of myeloid cancers
4. the anemia associated with the treatment of myeloid cancers or erythroid cancers
5. the anemia of cancer not related to cancer treatment
6. any anemia associated with radiotherapy
7. prophylactic use to prevent chemotherapy-induced anemia
8. prophylactic use to reduce tumor hypoxia
9. patients with erythropoietin-type resistance due to neutralizing antibodies
10. patients with treatment regimens including anti-angiogenic drugs such as bevacizumab
11. patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor
12. anemia due to cancer treatment if patients have uncontrolled hypertension
13. patients with thrombotic episodes related to malignancy

We also propose that ESA treatment is only reasonable and necessary under specified conditions for the treatment of anemia those types of cancer in which the presence of erythropoeitin receptors on either normal tissue/cell lines or malignant tissue/cell lines has been reported in the literature. These cancer types include but are not necessarily limited to:

- bone (sarcoma),
- brain-neurologic,
- breast,
- cervical,
- colo-rectal,
- gastric,
- head-and-neck (squamous cell),
- hepatic,
- lung,
- lymphoma
- melanoma,
- multiple myeloma
- muscle including cardiac,
- ovarian,
- pancreatic (exocrine),
- prostate,
- retinal, and
- uterine.

For patients undergoing treatment for these cancers, we propose that ESA use is reasonable and necessary with the following limitations:

1. the hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be < 9 g/dl/27% in patients without known cardiovascular disease and < 10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion (We suggest that patients, especially those in the latter category, be alerted to the increased potential for thrombosis and sequelae).
2. the maximum covered treatment duration is 12 weeks/year;
3. the maximum covered 4 week treatment dose is 126,000 units for erythropoietin and 630 µg for darbepoietin;
4. continued use of the drug is not reasonable and necessary if there is evidence of poor drug response (hemoglobin/hematocrit rise < 1 g/dl/< 3%) after 4 weeks of treatment;
5. continued administration of the drug is not reasonable and necessary if there is an increase in fluid retention or weight (5 kg) after 2 weeks of treatment; and
6. continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin/hematocrit > 1 g/dl/> 3% after 2 weeks of treatment.

Local contractors may continue to make reasonable and necessary determinations for all uses of ESA therapy for beneficiaries with cancer whose condition is not addressed above.

We are requesting public comments on this proposed determination pursuant to section 1862 as revised by 731 of the Medicare Modernization Act. In light of the issues discussed in our review of the evidence and serious safety concerns voiced in the May 10, 2007 FDA Oncologic Drugs Advisory Committee (ODAC) meeting we are also interested in public comment on whether coverage for ESA therapy for Medicare beneficiaries with cancer should occur only within appropriately designed clinical research studies where informed consent and safety monitoring can be assured. After considering the public comments and any additional evidence, we will make a final determination and issue a final decision memorandum.

Appendices [PDF, 2MB]
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